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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/532,708	03/22/2000	Sarita Kumari Jain	A-67933-1/RFT/RMS/DAV	8874

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Flehr Hohbach Test Albritton & Herbert LLP
Four Embarcadero Center
Suite 3400
San Francisco, CA 94111-4187

EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 09/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/532,708	JAIN ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-24,28,33 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-24,28,33 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This office action is in response to an amendment filed on August 13, 2003. Claims 12-24, 28, 33 and 49-51 were previously pending. Applicants cancelled claims 50 and 51. Claims 12-24, 28, 33 and 49 are pending and will be examined.

2. This office action is made non-final because of new grounds for rejection.

Claim interpretation

3. Before proceeding with the rejection some of the terms used in the claims will be interpreted.

A) The term "a library of target nucleic acid(s)" (claim 12) is interpreted as meaning any target nucleic acid, since Applicants did not define this term in the specification.

B) The term "a library of target nucleic acid variants" (claim 19) is interpreted as meaning any nucleic acid obtained by homologous recombination with target nucleic acid, since Applicants did not define this term in the specification.

C) The term "library of candidate agents" in claim 21 is interpreted as one or more agents of any origin.

D) A definition of separation moiety is provided by Applicants (page 22, lines 21-28):

> "By "separation moiety" or "purification moiety" or grammatical equivalents herein is meant a moiety which may be used to purify or isolate thenucleic acids, including the targeting polynucleotides, the targeting polynucleotidertarget sequence complex, or the target sequence. As will be appreciated by those in the art, the separation moieties may comprise any number of different entities, including, but not limited to, haptens such as chemical

moieties, epitope tags, binding partners, or unique nucleic acid sequences, basically anything that can be used to isolate or separate a targeting polynucleotide:target sequence complex from the rest of the nucleic acids present."

E) With respect to the robotic system, Applicants described the following components in the specification:

i) robotic system components for producing a plurality of enhanced homologous recombination (EHR) compositions and for contacting the EHR compositions with a cellular library: robotic system with a thermocycler, cooling position, automated pipettor, positions for tubes and plates (page 34, lines 11-39, page 35, line 1-29).

ii) components for isolating target nucleic acids: robotic system with an automated pipettor, positions for tubes and plates (page 35, lines 24-39); lines 31-39 describe manual isolation of DNA.

iii) components for producing a library of mutant nucleic acids: the process, described on page 43, lines 1-14, involves making a plurality of EHRs using a pool of targetting polynucleotides, each of which contains one or more mismatches. There is no description of how this is accomplished by a robotic system, and means for EHR formation using a robotic system were described on pages 34-35 (see above).

Claim Rejections - 35 USC § 103

4. Claims 12-20, 28, 33 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pati et al. (U.S. Patent No. 6,524,856) and Cathart et al. (WO 91/16675; cited in a previous office action).

A) Regarding claim 12, Pati et al. teach a method for targeting sequence modifications in a family of genes using homologous recombination (Abstract). In particular, Pati et al. teach a method comprising the steps

a) providing a plurality of enhanced homologous recombination (EHR) compositions, wherein each composition comprises:

i) a recombinase (Pati et al. teach coating of double stranded (ds) DNA probes with recombinase (Fig. 2; col. 8, lines 1-3; col. 12, lines 32-36; col. 16, lines 16-37));

ii) a first and a second targeting polynucleotide, wherein said first targeting polmucleotide comprises a portion substantially complementary to a fragment of a target nucleic acid and is substantially complementary tosaid second targeting polynucleotide (Pati et al. teach a plurality of EHR compositions comprising target nucleic acids from a mixture of nucleic acids, two-single stranded targeting polynucleotides which are substantially complementary to each other and each has a homology clamp (= a portion substantially complementary to a fragment of a target nucleic acid) for target nucleic acids from a gene family; see col. 4, lines 31-37; col. 13, lines 11-16 and 35-45; col. 14, lines 15-21 and 64-67); and

iii) a separation moiety (Pati et al. teach targeting polynucleotides with attached purification tags; see col. 4, lines 37-42;col. 23, lines 9-14; col. 26, lines 1-13);

b) contacting said EHR compositions with a library of target nucleic acid(s) under conditions wherein said targeting polynucleotides hybridize to one or more target nucleic acids of said library (Pati et al. teach contacting EHR compositions with a library of target nucleic acids; see Fig. 2; col. 30, lines 1-5); and

c) isolating and cloning said target nucleic acid(s) (Pati et al. teach isolation of the target nucleic acids by binding biotin to targeting polynucleotides and isolating target nucleic acid: targeting polynucleotide complex using streptavidin-coated magnetic beads and cloning of the isolated genes (Fig. 2; col. 23, lines 9-14; col. 25, lines 52-58; col. 26, lines 1-13).).

Regarding claim 13, Pati et al. teach target nucleic acid being a target gene (col. 6, lines 47, 48; col. 25, lines 41-67; col. 26, lines 1-13 and 31-39).

Regarding claim 14, Pati et al teach target nucleic acid being a portion of a target gene, such as sequence encoding a protein domain (col. 6, lines 54-56; col. 13, lines 35-38).

Regarding claim 15, Pati et al. teach target nucleic acid being a regulatory sequence (col. 6, lines 47-50; col. 19, lines 19-33).

Regarding claim 16, Pati et al. teach target nucleic acids comprising disease allele (col. 29, lines 1-19). Pati et al. do not specifically teach single-nucleotide polymorphisms, but since a disease allele means a nucleic acid sequence which differs by at least one nucleotide from a wild-type sequence, single nucleotide polymorphisms are inherently disease alleles, therefore Pati et al. teach target nucleic acids comprising single-nucleotide polymorphisms.

Regarding claim 17, Pati et al. teach cDNA libraries (Fig. 2; col. 26, line6; col. 30, line 4), genomic DNA samples (col. 6, lines 47-54 and 61-64).

Regarding claims 18 and 49, Pati et al. teach germline and pathogen target sequences (col. 6, lines 61-64).

Regarding claim 19, Pati et al. teach making a library of variant nucleic acids by introduction of alterations in the target nucleic acids (col. 17, lines 29-67; col. 18, lines 14; col. 26, lines 14-30), introducing the library of nucleic acid variants into cellular library (col. 26, lines 40-67; col. 27, 28) and performing phenotypic screening on the cellular library (col. 29, lines 22-29).

Regarding claim 28, Pati et al. teach sequencing of target nucleic acids (col. 25, lines 59-60; col. 26, lines 12, 13).

B) Pati et al. do not teach using a robotic system for isolating and cloning target nucleic acids or for making a library of target nucleic acids, introducing the library into cells or performing a phenotypic screening.

C) Regarding claims 12, 20 and 33, Cathcart et al. teach a robotic system for performing molecular biology procedures comprising a liquid-handling instrument with a modular stations to support liquid containers, automated pipettor, heating and cooling stations, thermocycler and a magnetic separation station for performing DNA isolation, all controlled by a computer system (Abstract; page 6, third paragraph; page 7; page 8, paragraphs 1 and 2; Fig. 1; page 10-15; page 23, paragraphs 3, 4; page 24; page 25, paragraphs 1 and 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the robotic system of Cathcart et al. in a method of Pati et al. The motivation to do so, provided by Cathcart et al., would have been that robotic system provided genetic information from a DNA sample overnight, as compared to days (page 49, the last paragraph). As stated by Cathcart ".... it is concluded that a robotic liquid handling instrument according to the invention can be used successfully to automate specific human gene detection ... The manner of which this result is accomplished is simpler and faster than the manual methods typically employed. The individual liquid handling steps are executed with precision. Since operation is computer controlled the process can be performed consistently, reliably, and relentlessly providing a new opportunity for high sample throuput." (page 50, first paragraph).

In addition, as stated in MPEP 2144.04 [R-1], automating manual activity is not sufficient to distinguish over the prior art.

2144.04 [R-1] III. AUTOMATING A MANUAL ACTIVITY

> In re Venner, 262 F.2d 91, 95, 120 USPQ 193, 194 (CCPA 1958) (Appellant argued that claims to a permanent mold casting apparatus for molding trunk pistons were

> allowable over the prior art because the claimed invention combined "old permanent-mold structures together with a timer and solenoid which automatically actuates the known pressure valve system to release the inner core after a predetermined time has elapsed." The court held that broadly providing an automatic or mechanical means to replace a manual activity which accomplished the same result is not sufficient to distinguish over the prior art.).

5. Claims 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pati et al. (U.S. Patent No. 6,524,856) and Cathart et al. (WO 91/16675; cited in a previous office action) as applied to claim 12 above, and further in view of Ghai et al. (U.S. Patent No. 5,955,269; cited in a previous offica action).

A) Regarding claim 21, Pati et al. teach identification of novel target genes which can be used in screening of drug candidates (col. 25, lines 64-67) and making a plurality of target cells comprising mutant target nucleic acids (col. 26, lines 14-30 and 40-67; col. 27, 28).

Regarding claim 23, Pati et al. teach mutant target nucleic acids being a sequence knock-out (col. 17, lines 46-60; col. 25, lines 41-51).

Regarding claim 24, Pati et al. teach mutant target nucleic acids comprising insertions, deletions or combinations thereof (col. 18, lines 10-67; col. 19, lines 1-18).

Regarding claim 22, Cathcart et al. teach a robotic system for performing molecular biology procedures comprising a liquid-handling instrument with a modular stations to support liquid containers, automated pipettor, heating and cooling stations, thermocycler and a magnetic separation station for performing DNA isolation, all controlled by a computer system (Abstract; page 6, third paragraph; page 7; page 8, paragraphs 1 and 2; Fig. 1; page 10-15; page 23, paragraphs 3, 4; page 24; page 25, paragraphs 1 and 2).

B) Neither Pati et al. nor Cathcart et al. teach adding a library of candidate agents to the cells and determining the effect of candidate agents on the cells.

B) Regarding claim 21, Ghai et al. teach methods of screening for the presence of bioactive substances in food (= library of candidate agents) by testing for their ability to modify gene expression in cells in vitro (col. 2, lines 51-67) or in animal models (col. 3, lines 1-15). The assays measure expression of genes (col. 3, lines 66-67; col. 4, lines 1-12) or determine phenotypic changes in cells (col. 4, lines 33-39). Once the effects of the active compound have been determined, the compound can be isolated and purified (col. 4, lines 44-50).

Regarding claim 22, Ghai et al. teach that the cells can be cultured and assayed using a robotic device (col. 17, lines 18-30).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the robotic system of Cathcart et al. in a method of Pati et al. The motivation to do so, provided by Cathcart et al., would have been that robotic system provided genetic information from a DNA sample overnight, as compared to days (page 49, the last paragraph). As stated by Cathcart ".... it is concluded that a robotic liquid handling instrument according to the invention can be used successfully to automate specific human gene detection ... The manner of which this result is accomplished is simpler and faster than the manual methods typically employed. The individual liquid handling steps are executed with precision. Since operation is computer controlled the process can be performed consistently, reliably, and relentlessly providing a new opportunity for high sample throuput." (page 50, first paragraph).

In addition, as stated in MPEP 2144.04 [R-1], automating manual activity is not sufficient to distinguish over the prior art.

2144.04 [R-1] III. AUTOMATING A MANUAL ACTIVITY

> In re Venner, 262 F.2d 91, 95, 120 USPQ 193, 194 (CCPA 1958) (Appellant argued that claims to a permanent mold casting apparatus for molding trunk pistons were allowable over the prior art because the claimed invention combined "old permanent-mold structures together with a timer and solenoid which automatically actuates the

known pressure valve system to release the inner core after a predetermined time has elapsed." The court held that broadly providing an automatic or mechanical means to replace a manual activity which accomplished the same result is not sufficient to distinguish over the prior art.).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used the combined method of Cathcart et al. and Pati et al. to screen for candidate agents of Ghai et al. The motivation to do so, provided by Ghai et al., would have been that candidate agents determined in food were used to treat or prevent disease (Abstract; col. 2, lines 35-48).

6. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

TS

September 4, 2003

TS

JEFFREY FREDMAN
PRIMARY EXAMINER